

Vitamin D Supplementation and Total Mortality A Meta-analysis of Randomized Controlled Trials

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FROM ABSTRACT

Background

Ecological and observational studies suggest that low vitamin D status could be associated with higher mortality from life-threatening conditions including cancer, cardiovascular disease, and diabetes mellitus that account for 60% to 70% of total mortality in high-income countries.

We examined the risk of dying from any cause in subjects who participated in randomized trials testing the impact of vitamin D supplementation (ergocalciferol [vitamin D2] or cholecalciferol [vitamin D3]) on any health condition.

Methods

The literature up to November 2006 was searched without language restriction using the following databases: PubMed, ISI Web of Science (Science Citation Index Expanded), EMBASE, and the Cochrane Library.

Results

We identified 18 independent randomized controlled trials, including 57,311 participants.

Daily doses of vitamin D supplements varied from 300 to 2000 IU.

Conclusions

Intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates.

THESE AUTHORS ALSO NOTE:

"Ecological studies in North America have suggested that mortality from several potentially life-threatening chronic health conditions such as cancer, cardiovascular diseases, and diabetes mellitus would increase with increasing latitude, that is, with residence increasingly distant from the equator."

UV-B radiation is between wavelengths 280-315 nm.

UV-A radiation is between wavelengths 315-400 nm.

UV-B radiation reduces more rapidly than UV-A radiation with increasing distance from the equator and with winter.

UV-B radiation is necessary for the synthesis of vitamin D in the skin.

Vitamin D is also found in oily fish, eggs, and butter.

The physiologically active form of vitamin D is dihydroxyvitamin D3 (calcitriol).

Vitamin D receptors are found in various organs, and activation of these receptors induces cell differentiation and inhibits proliferation, invasiveness, angiogenesis, and metastasis. This reduces the genesis of cancer and reduces cardiovascular ischemic diseases.

This study design was the quantitative synthesis of randomized controlled trials that could contribute to evaluating the impact of vitamin D supplementation on death from any cause.

In this study, the outcome analysis was total mortality.

The supplementation evaluated was vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol).

RESULTS

These authors used 18 randomized controlled trials involving 57,311 participants with a mean follow-up of 5.7 years.

"The mean daily dose of vitamin D supplements varied from 300 IU to 2000 IU, but most of the daily doses were between 400 IU and 833 IU."

The results of the 18 trials indicated a "significant decrease in the risk of all-cause mortality with using vitamin D supplements." [A 7% decrease in all cause mortality]

COMMENT FROM AUTHORS

"Results of this meta-analysis of randomized controlled trials suggest that intake of vitamin D supplements may decrease total mortality during trial duration."

The effect on mortality was not likely to be due to calcium supplements, because the 5 trials that did not include calcium supplements had similar results to the trials that included both vitamin D and calcium supplements.

The intake of vitamin D supplements resulted in increases in serum 25-hydroxyvitamin D levels.

"Our results provide reassurance that at ordinary doses, long-term vitamin D supplementation does not seem to be associated with an overall adverse effect."

The physiologically active form of vitamin D (1,25 dihydroxyvitamin D [calcitriol]) acts as a hormone that affects skeletal and extra skeletal tissues, calcium homeostasis, bone formation, cellular proliferation and differentiation, immune system function, bile acid transport, rennin production, the endothelium and vascular walls, and the endocrine system. These effects "could reduce aggressiveness of cancerous processes and expansion of atheromatous lesions."

In conclusion, the intake of ordinary doses of vitamin D supplements is associated with decreases in total mortality rates.

THIS ARTICLE GENERATED THIS EDITORIAL, in part:

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The role of vitamin D in calcium and phosphorus homeostasis is well established.

"In the last several decades, many studies have documented nontraditional roles of vitamin D, as well as adverse consequences of vitamin D deficiency for a range of conditions, including bone health, cancer, cardiovascular disease, glucose intolerance, high blood pressure, some infectious diseases, multiple sclerosis, and type 2 diabetes mellitus."

"The results [from the above study] are remarkable; individuals who were randomized to vitamin D had a statistically significant 7% reduction in mortality from any cause. The reduction was 8% for studies for which the intervention was at least 3 years."

There is evidence that vitamin D influences both incidence and survival of cancer.

By increasing vitamin D intake with supplements, "we may be correcting a deficiency caused primarily by a lack of the natural source of vitamin D, which is from sun exposure."

"Vitamin D is used in numerous endocrine, autocrine, and perhaps paracrine systems, acting as an important regulator of gene expression."

"Vitamin D appears to be important in the regulation of cell proliferation and differentiation; thus, deficiencies could contribute to carcinogenesis."

Vitamin D has been shown to be critical for innate immunity and the production of antibiotic peptides, and thus deficiency could contribute to diseases such as tuberculosis.

"The Achilles' heel of the intricate vitamin D system is that the precursor molecule, cholecalciferol, is entirely dependent on sun exposure or dietary intake."

"As a species, we do not get as much sun exposure as we used to, and dietary sources of vitamin D are minimal."

"An increasing number of researchers from various fields have been arriving at the conclusion that the levels of vitamin D in many people are inadequate for optimal health."

The upper limit for vitamin D consumption for adults should be 10,000 IU/d.

"Individuals can make up to 20,000 IU/d of vitamin D from sun exposure, and no case of sun-induced vitamin D toxic effects have ever been documented."

Given the high probability of benefit for at least some of the many conditions that have been associated with vitamin D deficiency, and the low likelihood of harm, it seems prudent that physicians suggest supplementation.

The optimal level of 25-hydroxyvitamin D is about 30 to 40 ng/mL. However, "taking supplements of even 800 IU/d of vitamin D would not achieve a goal of 30 ng/mL."

Sun exposure greatly influences vitamin D levels.

"An individual with minimal sun exposure (eg, a nursing home resident) may require 1000 to 2000 IU/d to achieve levels of 30 to 40 ng/mL."

"Ideally, the form of vitamin D used should be cholecalciferol (vitamin D3) rather than ergocalciferol (vitamin D2), which may not be as effective."

KEY POINTS FROM DAN MURPHY

- 1) "Low vitamin D status could be associated with higher mortality from life-threatening conditions including cancer, cardiovascular disease, and diabetes mellitus that account for 60% to 70% of total mortality in high-income countries."
- 2) Vitamin D supplements are associated with decreases in total mortality rates.
- 3) UV-B radiation is between wavelengths 280-315 nm.
UV-A radiation is between wavelengths 315-400 nm.

- 4) UV-B radiation reduces more rapidly than UV-A radiation with increasing distance from the equator and with winter.
- 5) UV-B radiation is necessary for the synthesis of vitamin D in the skin.
- 6) Vitamin D is also found in oily fish, eggs, and butter.
- 7) The physiologically active form of vitamin D is dihydroxyvitamin D₃ (calcitriol).
- 8) This study showed that 5.7 years of supplementation with between 400 – 833 IU of vitamin D / day resulted in a 7% decrease in all cause mortality over that period of time.
- 9) Calcium supplements did not reduce all cause mortality, it was only the vitamin D that did so.
- 10) The intake of ordinary doses of vitamin D supplements is associated with decreases in total mortality rates.
- 11) Vitamin D is important in calcium and phosphorus homeostasis, bone health, cancer, cardiovascular disease, diabetes, some infectious diseases, multiple sclerosis, and type-2 diabetes mellitus.
- 12) In this study," individuals who supplemented with vitamin D had a statistically significant 7% reduction in mortality from any cause, and the reduction was 8% for those who supplemented for at least 3 years."
- 13) Vitamin D influences both incidence and survival of cancer.
- 14) Vitamin D has been shown to be critical for innate immunity and the production of antibiotic peptides, and thus deficiency could contribute to diseases such as tuberculosis.
- 15) "As a species, we do not get as much sun exposure as we used to, and dietary sources of vitamin D are minimal."
- 16) Given the high probability of benefit for at least some of the many conditions that have been associated with vitamin D deficiency, and the low likelihood of harm, it seems prudent that physicians suggest supplementation.
- 17) "An individual with minimal sun exposure (e.g. a nursing home resident) may require 1000 to 2000 IU/d to achieve levels of 30 to 40 ng/mL."
- 18) "Ideally, the form of vitamin D used should be cholecalciferol (vitamin D₃) rather than ergocalciferol (vitamin D₂), which may not be as effective."